Immunity to varicella-zoster virus in immunocompromised patients

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Summary, discussion and future perspectives

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SUMMARY

Immunocompromised persons are at increased risk of herpes zoster and its complications. To date, only one herpes zoster vaccine is licensed for use. Essentially, this vaccine is contraindicated in immunosuppressed persons. The Advisory Committee on Immunization Practices (ACIP) formulated recommendations for use of the vaccine in immunosuppressed patient groups, however, based on expert opinion only [1]. To increase the understanding of the increased herpes zoster risk, we investigated immunity to the varicella-zoster virus in immunocompromised patient groups.

Chapter 1 provides a general introduction to the thesis. The varicella-zoster virus (VZV), its pathogenesis, epidemiology, clinical manifestations and vaccination as a preventive measure are addressed. The use of vaccination to prevent herpes zoster in immunocompromised patients is discussed, as well as the disorders associated with an immunocompromised state that are addressed in this thesis.

Part I of the thesis describes experimental studies of humoral and cellular immunity to VZV in immunocompromised patient groups. Chapter 2 discourses on VZV immunity in patients with systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (GPA). No differences in VZV-specific immunity were found between GPA patients and matched healthy controls, while T cells of GPA patients were shown to have a generally decreased proliferating capacity (in response to polyclonal stimulation). In SLE patients cellular immunity to VZV, as determined by interferon-γ (IFNγ) enzyme-linked immunosorbent spot (ELISpot) assay and T cell proliferation assay, was shown to be decreased compared to healthy controls (HC). Influence of medication use was not seen. In contrast to cellular immunity, levels of VZV-specific IgG were higher in SLE patients than in healthy controls. As decreased IgG antibody levels were found against diphtheria, antibody levels were not increased for all specific antigens in SLE. Diphtheria was chosen as this disease is non-endemic in The Netherlands.

Especially cellular immunity is considered to be of importance in the immunologic defence against herpes zoster, and the decreased cellular immunity to VZV in SLE patients could explain the increased herpes zoster risk in these patients. However, we were interested in the cause of the increased VZV-IgG antibody level in SLE patients. In chapter 3, we studied the humoral immune response to VZV in SLE patients in greater detail. We hypothesized that the increased VZV-IgG level was a result of subclinical reactivation of the latently present VZV and that these reactivations were potentiated by stress caused by lupus disease activity or immunosuppressive medication. VZV-specific IgG, IgA and IgM levels, levels of total IgG and presence of VZV-DNA in SLE patients were longitudinally observed. Using a predefined definition, we found subclinical VZV reactivations to occur infrequently in these patients, all of whom had established disease. Using GEE analysis, which was independent from our definition of a subclinical reactivation, we did not find an association between VZV antibody levels and lupus disease activity or medication use. We therefore did not find proof supporting our hypothesis.

In **chapter 4** we investigated VZV-specific immunity in patients with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR). VZV has been suggested to be involved in the pathogenesis of GCA. A decreased cellular immunity to VZV was observed in GCA patients using an IFNγ ELISpot assay, compared to an age-matched elderly healthy control group, but not in PMR patients. GCA patients are therefore expected to be at higher risk of herpes zoster. Humoral immunity to VZV was similar in GCA patients, PMR patients and healthy controls. This may indicate that herpes zoster did not occur substantially more often in GCA and PMR patients in the months preceding diagnosis, than in controls.

Chapter 5 describes VZV-specific immunity in patients in need of long-term renal replacement therapy, who are considered to be immunocompromised because of their uraemic state. Multiple linear regression analysis revealed that age and a history of renal transplantation were associated with a decreased cellular immunity, as assessed with an IFNγ ELISpot assay. As a higher herpes zoster risk has been reported in patients treated with peritoneal dialysis than in those treated with haemodialysis, we also included treatment modality in the analysis. The proportion of IFNγ producing cells in response to stimulation with VZV did not significantly differ between patients treated with haemodialysis or peritoneal dialysis, also after correcting for age. The percentage of T cells producing cytokines (IFNγ, tumour necrosis factor α and interleukin-2) was increased in dialysis patients, both following VZV-specific and polyclonal stimulation. T cells of patients and control were equally capable of proliferating, both in response to stimulation with VZV and polyclonal stimulation. The regression model that was used to assess factors of influence (age, gender, transplant history, treatment modality and urea levels) on humoral immunity in dialysis patients did not statistically significantly predict VZV-IgG levels. As we did not find measures of cellular or humoral immunity to be decreased in dialysis patients compared to controls, we are not able to sufficiently explain the increased herpes zoster risk in these patients at this moment. Zoster susceptibility may be due to a diminished function of otherwise capable T cells in a uraemic environment.

In **chapter 6** we studied changes in VZV immunity that occur after renal transplantation. No marked changes in cellular immunity to VZV following renal transplantation were observed. Transplant recipients however were shown to have a lower cellular immunity to VZV than matched control subjects, corresponding with a high herpes zoster risk in these patients. Cellular immunity to VZV seemed to be especially low in transplant recipients that experienced rejection or any infection in the post-transplant period. Difference in cellular immunity against VZV was significant in patients who experienced infection post-transplantation compared to those who did not. The high percentages of cytokine-producing T cells before transplantation, following both VZV-specific and polyclonal stimulation, were no longer present after transplantation. No differences in functionality of T cells were observed before and after transplantation, and between transplant recipients and controls, as assessed by comparing percentages of cells concomitantly producing more than 1 cytokine and expression of functional anergy

markers programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). In contrast to cellular immunity, humoral immunity to VZV was shown to decrease significantly following transplantation, but resulting levels were not different from levels in healthy control subjects.

Part II of the thesis starts with a literature review on vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD) (**chapter 7**). Epidemiology of vaccine-preventable infectious diseases, and both the efficacy and safety of vaccination to prevent these diseases in patients with an autoimmune inflammatory rheumatic disease were addressed.

In **chapter 8**, we formulated a proposal for updated European recommendations for the use of vaccination in AIIRD patients. We focused specifically on efficacy of vaccination in AIIRD. After a systematic literature search, and a discussion meeting of a multidisciplinary international expert committee, the proposed recommendations were formulated.

GENERAL DISCUSSION

In the studies described in this thesis we evaluated immunity to VZV in several immunosuppressed patient groups, known to be at risk of herpes zoster. Our results underline the importance of cellular immunity in keeping the latently present VZV in check. A decreased cellular immunity to VZV in several patient groups was revealed: systemic lupus erythematosus (SLE, **chapter 2**), giant cell arteritis (GCA, **chapter 4**) and renal transplant recipients (**chapter 5/6**), while humoral immunity was not found to be impaired. Our results are in line with studies that also reported decreased cellular immunity, determined by an IFNγ ELISpot assay, for other groups at risk for herpes zoster, including the elderly [2], patients with diabetes mellitus [3], HIV-infected patients [4] and patients with haematological malignancies [5].

The IFNγ enzyme-linked immunosorbent spot (ELISpot) assay method is the most frequently used assay to investigate cellular immunity to VZV in the aforementioned reports [2-5] and throughout this thesis. The ELISpot assay is generally regarded as a reliable method when assessing cellular immunity to VZV [6,7]. However, when assessing cellular immunity to VZV in dialysis patients, known to be at high risk of herpes zoster [8-11], ELISpot assay did not show a lower number of IFNγ spot-forming cells in dialysis patients compared to healthy controls (**chapter 5**). In these patients a pro-inflammatory milieu exists, caused by uraemia and accompanied by hypercytokinaemia. Future studies should keep in mind that ELISpot test results do not seem to correspond with herpes zoster risk in dialysis patients.

Medication use and herpes zoster risk

In **chapter 7** we concluded from a systematic literature review that medication use is associated with a higher zoster risk in patients with AIIRD (rheumatoid arthritis [RA], SLE, GPA), with the exception of etanercept and methotrexate. With a relative risk of over 4, cyclophosphamide entails the highest relative risk of the investigated drugs. In **chapter 2** however, we did not find an influence of medication use on VZV immunity in SLE and GPA patients, although a trend towards a higher VZV antibody level was found among GPA patients using immunosuppressive medication compared to those who did not. The absence of a medication effect could be due to the limited number of included patients, and the large proportion of patients with quiescent disease, corresponding with limited use and dosages of immunosuppressive agents. Also in **chapter 3**, we did not find a medication effect on levels of VZV-specific antibody levels in SLE patients when performing a longitudinal analysis, while we did clearly show an effect of different immunosuppressive drugs on total IgG levels.

In **chapter 4** we speculated that the decreased cellular immunity to VZV in GCA patients is caused by use of high doses glucocorticoids, known to be a risk factor for herpes zoster (**chapter 7**). This seems to be confirmed by the observation that cellular immunity to VZV in patients with PMR is not impaired. PMR is a disease that frequently

overlaps with GCA, but is treated with lower doses of glucocorticoids. Also in **chapter 5** we found evidence for a medication effect on VZV-specific immunity. In this chapter we demonstrated that a history of transplantation is associated with an impaired cellular immunity to VZV. This can be explained by intensive use of immunosuppressive medication surrounding transplantation, and can even be elevated further by anti-rejection therapy, as in these cases a low VZV-specific cellular immunity (**chapter 6**) and an increased herpes zoster risk is found [9,12]. Interestingly, we showed that this effect lasts for many months after cessation of immunosuppressive therapy.

In recent years, anti-interferon (IFN) α therapy has been introduced in SLE patients. This therapy has been linked to an increased herpes zoster risk, which can be explained by the importance of type 1 IFN in mediating the initial innate immune response to VZV, as addressed in the introduction of this thesis [13-15]. Also inhibitors of Janus kinase (JAK) are new in the treatment of rheumatic diseases. JAK, in combination with cytokine receptors and signal transducers and activators of transcription (STAT), transmits extracellular cytokine signals to activate pro-inflammatory responses within the cell. As also the innate antiviral response via type 1 IFN is mediated by JAK, JAK inhibition leads to an increased herpes zoster risk [16]. Live zoster vaccination in RA patients treated with tofacitinib, the first JAK inhibitor that was commercially approved, was shown to lead to similar increases in humoral and cellular immunity against VZV as in RA patients treated with placebo [17]. However, influence of zoster vaccination on long-term incidence of herpes zoster in patients treated with tofacitinib is not yet clear.

In general, prescribers would ideally vaccinate patients before initiating therapy that is associated with an increased risk of herpes zoster. This timing would be ideal as vaccination then would precede increased medication associated zoster risk. Furthermore, vaccination before initiation of therapy may be safer and more efficacious. Vaccination before initiation of therapy is not always possible. Temporary suspending medication surrounding vaccination may then be an option in stable patients, but needs to be further investigated. In RA patients temporary discontinuation of methotrexate was shown to improve immunogenicity of seasonal influenza vaccination in patients with RA, with the best results when methotrexate was suspended for 2 weeks before and 2 weeks after vaccination [18].

Choice of zoster vaccine in immunocompromised patients

The live attenuated zoster vaccine has been shown to increase humoral and cellular immunity to VZV in the elderly and to decrease the risk of herpes zoster by 37.6% to 63.9% dependent on age group [19,20]. Recently, a new, not yet licensed zoster subunit vaccine has been shown to increase VZV-specific immune responses, but with higher efficacy. Vaccine efficacy was between 91.3% and 97.9%, and was not significantly different between age groups [21,22]. There is a major difference between the two vaccines: the currently only used vaccine contains live attenuated micro-organisms, while

the new, not yet licensed, vaccine is a subunit vaccine that contains an adjuvant system. As we showed (in **chapters 2, 4 and 6**) that cellular immunity (in general and in response to VZV) is impaired in immunocompromised patient groups and efficacy of several vaccines has been shown to be lower in certain groups of immunocompromised patients (**chapter 7**), it may also be harder to elicit a sufficient immune response to the zoster vaccine in these groups. Both because of higher efficacy and absence of live attenuated virus, the subunit vaccine seems to be an attractive candidate-vaccine especially in patients with an impaired immune system.

The recombinant subunit vaccine contains VZV envelope glycoprotein E (gE) and adjuvant system AS01. VZV gE was chosen as an antigen, as it is the primary target for the immune response to VZV. It is the most abundant glycoprotein on the surface of infected cells and essential in VZV pathogenesis [23]. Without an adjuvant, recombinant subunit vaccines do not lead to satisfactory immune responses. After the discovery that certain substances could improve immune response, in the 1930s the first adjuvant used in vaccines was aluminium. However, aluminium was found to be insufficient to induce the desired immune response in vaccines against certain pathogens (e.g. human immunodeficiency virus (HIV), malaria) and researchers started to test other substances and combinations of substances.

The adjuvant system AS01 is a combination of immunostimulants QS-21 (*Quillaja saponaria* Molina: fraction 21) and MPL (3-deacylated monophosphoryl lipid) with liposomes [24]. QS-21 is extracted from the bark of the *Quillaja saponaria* tree and MPL is a detoxified derivative of bacterial lipopolysaccharide (LPS), which can activate the innate immune system via toll-like receptor 4 (TLR-4) [25]. AS01 has been shown to lead to greater enhancement of the CD4+ T cell response to gE than other adjuvant systems when tested in mice [26]. Among other effects, it has been shown to increase the number of antigen presenting cells (APC) and the expression of costimulatory molecules on these cells, that are able to activate T cells in the draining lymph node. Thereby it contributes to the generation of particularly a strong cellular immune response [27].

To date, immunogenicity and safety of the subunit vaccine have been investigated in young and older adults, HIV-infected persons and autologous hematopoietic cell transplant recipients. Although in the latter group one case of pneumonia was thought to be possibly vaccine related by the investigator, the vaccine was generally found to be effective and to be tolerated well [21,22,28-30].

To the best of our knowledge, safety of the AS01 or AS02 (which also contains MPL and QS-21 but is emulsion- instead of liposome-based) adjuvant system has not been investigated in patients with autoimmune inflammatory rheumatic diseases (AIIRD) or in animal models of autoimmune diseases. One could speculate that a substance that is potent in inducing strong immune responses also could have a detrimental effect on AIIRD activity, by reactivating the disease. Experimental T cell-mediated autoimmune diseases can develop if self-antigens are administered with strong adjuvants [31]. Adjuvants

have been suggested to be able to induce a variety of clinical symptoms, covered in a syndrome termed ASIA (Autoimmune/inflammatory Syndrome Induced by Adjuvants). The mechanisms by which adjuvants could lead to, or to exacerbate, autoimmune diseases are thought to be similar to the ones in which infectious agents are thought to be able to lead to autoimmunity [32]. These mechanisms are discussed later in this discussion in the paragraph on the role of VZV in the pathogenesis of AIIRD. The base of evidence for the proposed detrimental but rare effects of adjuvants is not strong, mainly consisting of case reports and experiments in animal models resulting in ambiguous results [33].

As both the live attenuated and the adjuvanted subunit zoster vaccines are accompanied with specific (rare) risks, pros and cons of both should be weighed in the individual patient. Further investigations should help find the balance between the risks and benefits of both vaccines in immunocompromised patients and patients with AIIRD.

Herpes zoster vaccination in patients with renal diseases

Vaccination using a live attenuated zoster vaccine has been shown to reduce the risk of herpes zoster by half in renal dialysis patients, with a risk of 11.7 per 1000 person-years in vaccinated patients [11]. This risk is, however, still higher than the estimated risk in immunocompetent persons over 80 years of age [34]. In **chapter 5** we showed that VZV specific T cells of dialysis patients are able to respond to VZV stimulation with the production of cytokines. We speculated that zoster susceptibility in these patients may be due to a diminished function of otherwise capable T cells in a uraemic environment.
As has previously been shown in studies of influenza vaccination, maintenance of specific T-cell memory in patients with end-stage renal failure is impaired [35]. The with time declining effect of live attenuated zoster vaccine which is also present in healthy elderly, can therefore be expected to be even larger in dialysis patients [36]. It would be very interesting to study the adjuvanted subunit vaccine in dialysis patients, which has been shown to be more efficacious but also to have longer lasting immunogenicity than the live attenuated vaccine [37]. When licensed, the subunit vaccine might be an alternative to live attenuated zoster vaccine in renal transplant recipients, which are considered too severely immunosuppressed to receive live attenuated vaccines. Until that time, vaccinating chronic kidney disease patients before transplantation with a live attenuated vaccine could have some effect in reducing herpes zoster risk after transplantation, as discussed in **chapter 6**. VZV cellular immunity did not decline to a large extent in the years after transplantation. Finally, taking measures to prevent herpes zoster may be of particular importance in patients with a history of transplantation and rejection due to their impaired cellular immunity to VZV (**chapter 5/6**).

Options in herpes zoster prevention other than vaccination

Other options in herpes zoster prevention than vaccination may be useful in persons at risk of herpes zoster, but in whom vaccination is contra-indicated.

Low doses antivirals acyclovir and valacyclovir were successfully used to prevent herpes zoster in oncology patients that were undergoing antineoplastic therapy [38]. However, in patients in whom herpes zoster risk is high for a prolonged period of time, like the patient groups discussed in this thesis, this method is not practical due to potential side-effects, costs and the risk of resistance.

Also other substances might aid in the prevention of herpes zoster in high-risk patients in whom vaccination is not possible. Examples of substances that that are suggested to have antiviral potency include glycyrrhizin, resveratrol and orlistat. Like QS-21 (the adjuvant used in the subunit zoster vaccine) glycyrrhizin is a saponin. Saponins are present in plants and trees, and are considered to have microbial activity [39,40]. Antiviral capacity of glycyrrhizin, present in liquorice, probably results from direct inhibition of high mobility group box 1 (HMGB1). HMGB1 is a nuclear protein, which has pro-inflammatory effects when present extracellularly [41]. Several viral infections have been shown to trigger HMGB1 release [42,43]. Also resveratrol, shown to inhibit the migration of HMGB1 out of the nucleus during dengue virus infection, has antiviral activity [43].

Orlistat is registered as an anti-obesity drug, but has recently been shown also to have antiviral activity. In VZV-infected lung fibroblasts, it reduced viral replication. Orlistat is thought to work by reducing enzymatic activity of fatty acid synthase, which not only is involved in the regulation of metabolic processes in human cells, but is also involved in replication of different viruses [44].

Efficacy and side-effects of these and other substances that may have anti-viral capacity needs to be studied further before they can be used in persons at high-risk of herpes zoster.

Role of VZV in the pathogenesis of autoimmune inflammatory rheumatic diseases

The development of an immune response to self is thought to be a result of multiple factors, including genetics, age and environment. Viral and bacterial infections may contribute to development and exacerbation of autoimmunity. Usually the micro-organism is not present at the site of autoimmune inflammation or detectable in the individual when autoimmunity develops. It is therefore believed that autoimmune inflammation is not due to the infectious agent itself, but is a result of host immune responses that are dysregulated by the micro-organism. Several mechanisms are possible. Micro-organisms for instance may contain antigens that are similar to self-antigen, so immune responses to the microbe may result in reactions against self-antigen, which is termed ‘molecular mimicry’. Another possible mechanism is ‘epitope spreading’. Herein the tissue damage that results from an immune response to a persistent pathogen leads to the exposure of self-antigens that are normally concealed from the immune system. ‘Bystander activation’ stands for the indirect or non-specific activation of autoimmune cells as a result of the inflammatory environment during infection. Lastly, negative selection of autoreactive

T cells usually occurs when they recognize self-epitopes, normally found in high concentrations on the surface of APC in association with MHC (major histocompatibility complex). However, when these self-antigens are present on APC in low concentration, they are termed 'cryptic' and will not results in removal of autoreactive T cells, but instead autoimmunity is triggered [31,45].

Also for varicella-zoster virus clues have been found for a role in the initiation and exacerbations of autoimmune diseases. Recent studies suggested an etiologic role of VZV in giant cell arteritis (GCA). It is hypothesized that an unknown specific antigen activates immature dendritic cells residing in the adventitia as a first step in the inflammatory cascade of GCA [46-48]. The finding of VZV antigen in temporal artery biopsies of a majority of GCA patients is seen as the pivotal evidence claiming an etiologic role for VZV in GCA. Also, VZV-DNA was detected in temporal arteries from GCA patients, although at lower frequencies [49-51]. 'Bystander activation' after original VZV vasculopathy might therefore be the underlying mechanism of GCA. However, other research groups were not able to find VZV antigen or DNA in temporal arteries of GCA patients [52-55]. Pathologists uttered concerns about the possibly false-positive detection of VZV in temporal arteries due to antibody cross-reactivity with muscular elements [56]. Although in a retrospective database study GCA cases were more likely to have had a prior herpes zoster infection, also other antecedent infections were more common, and the association was only modest [57]. In **chapter 4** we report similar humoral immunity in healthy persons, GCA patients and PMR patients. As it is known that VZV-specific IgG levels only slowly decline after herpes zoster [20,58,59], increased levels of VZV-IgG supposedly would have been found in patients at time of GCA diagnosis if VZV was involved in its pathogenesis. Realizing this is only circumstantial evidence and we did not investigate the presence of VZV at the site of inflammation, we think this information adds to the existing evidence that questions the proposed etiologic role of VZV in the pathogenesis of GCA.

Viral infections have also been suggested to be involved in initiation of disease and relapsing nature of systemic lupus erythematosus (SLE). In **chapter 2** we reported increased antibody levels and impaired cellular immunity to VZV in SLE. Similar results have been reported for Epstein-Barr virus (EBV), which for decades has been suspected to be contributing to development of SLE, although the mechanistic link remains unclear [60,61]. EBV-reactivations were thought to be causative of elevated levels of EBV-DNA and antibodies directed against lytic cycle antigens in SLE patients, and also to contribute to occurrence of lupus disease flares [62]. Indeed, EBV viral load was found to be higher in patients with active disease, although this seems to be more a result from lupus disease than the other way around [63]. In **chapter 3** we looked for an association between lupus disease activity and VZV, which was absent. This makes a contributing role of VZV in relapsing course of SLE seem unlikely.

FUTURE PERSPECTIVES

In the studies described in this thesis, steps have been made towards optimising preventive measures for herpes zoster in immunocompromised patients by increasing knowledge on immunity to VZV and the mechanism by which herpes zoster risk is increased in these patients. Still, more steps have to be made before these findings can lead to better prevention of herpes zoster in clinical practice. Throughout the general discussion, opportunities for future research came to light, of which some will be highlighted here.

Our research group will continue to work on VZV in immunocompromised persons. Among other projects, currently work is done evaluating efficacy of the live attenuated zoster vaccine in patients awaiting lung transplantation.

In the coming years, efficacy and safety of the new subunit zoster vaccine in immunosuppressed patient groups deserve attention, including safety of the adjuvant system AS01 in patients with autoimmune diseases, as indicated in the general discussion. Of special interest are patients treated with anti-IFN therapy and JAK inhibitors, who are at increased risk of herpes zoster, as explained previously in this discussion.

The epidemiology of herpes zoster was suggested to change in countries where routine varicella vaccination is given. Contact with infectious children is thought to be a natural exogenous booster of VZV immunity in seropositive individuals. If due to routine vaccination, varicella in children does not longer occur, this exogenous boosting will also not take place. To date, contradicting results are reported on herpes zoster epidemiology following routine varicella vaccination in the involved countries [64,65]. Herpes zoster incidence in children that were vaccinated as a child is also matter of debate. Although herpes zoster seems to be less common in vaccinated children, effects on longer term are not known [66]. For The Netherlands, where both varicella and zoster vaccination are not routinely recommended, it would be interesting to see developments in other countries and, if necessary, to adjust current policy.

Lastly, in smaller groups of immunocompromised subjects, it is hard to execute herpes zoster vaccination studies based on clinical endpoints. A uniform correlate of protection would be very useful in future studies. Determining humoral immunity is not of worth when predicting herpes zoster risk in a VZV-seropositive individual. In this thesis and in other reports investigating immunity to VZV, an IFNγ ELISpot assay is frequently used. Laboratory protocols and settings of ELISpot readers may differ between studies. It would be useful to have a more uniform method of establishing cellular immunity to VZV that yields the same results in different laboratories, and to make a risk classification for the occurrence of herpes zoster based on a laboratory method. An enzyme-linked assay (ELISA) that measures IFNγ in the supernatant of PBMC cell culture may be a candidate in reaching this goal [68].

REFERENCES

1. Harpaz R, Ortega-Sanchez IR, Seward JF, Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008;57:1,30; quiz CE2-4.
2. Shirane R, Tang H, Hayashi K, Okuno Y, Iso H, Asada H, et al. Relationship between cell-mediated immunity to Varicella-Zoster virus and aging in subjects from the community-based Shozu Herpes Zoster study. J Med Virol 2017;89:313-7.
3. Okamoto S, Hata A, Sadaoka K, Yamanishi K, Mori Y. Comparison of varicella-zoster virus-specific immunity of patients with diabetes mellitus and healthy individuals. J Infect Dis 2009;200:1606-10.
4. De Castro N, Carmagnat M, Kerneis S, Scieux C, Rabian C, Molina JM. Varicella-zoster virus-specific cell-mediated immune responses in HIV-infected adults. AIDS Res Hum Retroviruses 2011;27:1089-97.
5. Kim JW, Min CK, Mun YC, Park Y, Kim BS, Nam SH, et al. Varicella-zoster virus-specific cell-mediated immunity and herpes zoster development in multiple myeloma patients receiving bortezomib- or thalidomide-based chemotherapy. J Clin Virol 2015;73:64-9.
6. Lehmann PV, Zhang W. Unique strengths of ELISPOT for T cell diagnostics. Methods Mol Biol 2012;792:3-23.
7. Karlsson AC, Martin JN, Younger SR, Bredt BM, Epling L, Ronquillo R, et al. Comparison of the ELISPOT and cytokine flow cytometry assays for the enumeration of antigen-specific T cells. J Immunol Methods 2003;283:141-53.
8. Kuo CC, Lee CT, Lee IM, Ho SC, Yang CY. Risk of herpes zoster in patients treated with long-term hemodialysis: a matched cohort study. Am J Kidney Dis. 2012;59:428-33.
9. Lin SY, Liu JH, Lin CL, Tsai IJ, Chen PC, Chung CJ, et al. A comparison of herpes zoster incidence across the spectrum of chronic kidney disease, dialysis and transplantation. Am J Nephrol 2012;36:27-33.
10. Wu MY, Hsu YH, Su CL, Lin YF, Lin HW. Risk of herpes zoster in CKD: a matched-cohort study based on administrative data. Am J Kidney Dis 2012;60:548-52.
11. Tseng HF, Luo Y, Shi J, Sy LS, Tartof SY, Sim JJ, et al. Effectiveness of Herpes Zoster Vaccine in Patients 60 Years and Older With End-stage Renal Disease. Clin Infect Dis 2016;62:462-7.
12. Pavlopoulou ID, Poulopoulou S, Melexopoulou C, Papazaharia I, Zavos G, Boletis IN. Incidence and risk factors of herpes zoster among adult renal transplant recipients receiving universal antiviral prophylaxis. BMC Infect Dis 2015;15:285,015-1038-1.
13. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis Rheumatol 2017;69:376-86.
14. Kirou KA, Gkrouzman E. Anti-interferon alpha treatment in SLE. Clin Immunol 2013;148:303-12.
15. Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, et al. Sifalimumab, an anti-interferon-alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis 2016;75:1909-16.
16. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol 2017;13:234-43.

17. Winthrop KL, Wouters AG, Choy EH, Soma K, Hodge JA, Nduaka CI, et al. The Safety and Immunogenicity of Live Zoster Vaccination in Patients With Rheumatoid Arthritis Before Starting Tofacitinib: A Randomized Phase II Trial. Arthritis Rheumatol 2017.

18. Park JK, Lee MA, Lee EY, Song YW, Choi Y, Winthrop KL, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis 2017.

19. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271-84.

20. Weinberg A, Zhang JH, Oxman MN, Johnson GR, Hayward AR, Caulfield MJ, et al. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. J Infect Dis 2009;200:1068-77.

21. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015;372:2087-96.

22. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Diez-Domingo J, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med 2016;375:1019-32.

23. Cunningham AL. The herpes zoster subunit vaccine. Expert Opin Biol Ther 2016;16:265-71.

24. Garcon N, Di Pasquale A. From discovery to licensure, the Adjuvant System story. Hum Vaccin Immunother 2017;13:19-33.

25. Garcon N, Van Mechelen M. Recent clinical experience with vaccines using MPL- and QS-21-containing adjuvant systems. Expert Rev Vaccines 2011;10:471-86.

26. Fochesato M, Dendouga N, Boxus M. Comparative preclinical evaluation of AS01 versus other Adjuvant Systems in a candidate herpes zoster glycoprotein E subunit vaccine. Hum.Vaccin Immunother 2016;12:2092-5.

27. Didierlaurent AM, Collignon C, Bourguignon P, Wouters S, Fierens K, Fochesato M, et al. Enhancement of adaptive immunity by the human vaccine adjuvant AS01 depends on activated dendritic cells. J Immunol 2014;193:1920-30.

28. Leroux-Roels I, Leroux-Roels G, Clement F, Vandepapeliere P, Vassilev V, Ledent E, et al. A phase 1/2 clinical trial evaluating safety and immunogenicity of a varicella zoster glycoprotein e subunit vaccine candidate in young and older adults. J Infect Dis 2012;206:1280-90.

29. Stadtmauer EA, Sullivan KM, Marty FM, Dadwal SS, Papanicolaou GA, Shea TC, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. Blood 2014;124:2921-9.

30. Berkowitz EM, Moyle G, Stellbrink HJ, Schurmann D, Kegg S, Stoll M, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis 2015;211:1279-87.

31. Abbas AK, Lichtman AH, Pillai S. Ch. 18 - Diseases caused by immune responses: hypersensitivity and autoimmunity. Cellular and molecular immunology. 6th ed.: Saunders Elsevier; 2010. p. 419-39.

32. Pellegrino P, Clementi E, Radice S. On vaccine's adjuvants and autoimmunity: Current evidence and future perspectives. Autoimmun Rev 2015;14:880-8.

33. Guimaraes LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. Pharmacol Res 2015;100:190-209.

34. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther AdvVaccines 2015;3:109-20.

35. Sester U, Schmidt T, Kuhlmann MK, Gartner BC, Uhlmann-Schiffler H, Sester M. Serial influenza-vaccination reveals impaired maintenance of specific T-cell memory in patients with end-stage renal failure. Vaccine 2013;31:4111-20.

36. Morrison VA, Johnson GR, Schmader KE, Levin MJ, Zhang JH, Looney DJ, et al. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 2015;60:900-9.

37. Chlibek R, Pauksens K, Rombo L, van Rijckevorsel G, Richardus JH, Plassmann G, et al. Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults. Vaccine 2016;34:863-8.

38. Sandherr M, Hentrich M, von Lilienfeld-Toal M, Massenkeil G, Neumann S, Penack O, et al. Antiviral prophylaxis in patients with solid tumours and haematological malignancies--update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Ann Hematol 2015;94:1441-50.

39. Arabski M, Wegierek-Ciuk A, Czerwonka G, Lankoff A, Kaca W. Effects of saponins against clinical E. coli strains and eukaryotic cell line. J Biomed Biotechnol 2012;2012:286216.

40. Avato P, Bucci R, Tava A, Vitali C, Rosato A, Bialy Z, et al. Antimicrobial activity of saponins from Medicago sp.: structure-activity relationship. Phytother Res 2006;20:454-7.

41. Mollica L, De Marchis F, Spitaleri A, Dallacosta C, Pennacchini D, Zamai M, et al. Glycyrrhizin binds to high-mobility group box 1 protein and inhibits its cytokine activities. Chem Biol 2007;14:431-41.

42. Hosakote YM, Brasier AR, Casola A, Garofalo RP, Kurosky A. Respiratory Syncytial Virus Infection Triggers Epithelial HMGB1 Release as a Damage-Associated Molecular Pattern Promoting a Monocytic Inflammatory Response. J Virol 2016;90:9618-31.

43. Zainal N, Chang CP, Cheng YL, Wu YW, Anderson R, Wan SW, et al. Resveratrol treatment reveals a novel role for HMGB1 in regulation of the type 1 interferon response in dengue virus infection. Sci Rep 2017;7:42998.

44. Ammer E, Nietzsche S, Rien C, Kuhnl A, Mader T, Heller R, et al. The anti-obesity drug orlistat reveals anti-viral activity. Med Microbiol Immunol 2015;204:635-45.

45. Ercolini AM, Miller SD. The role of infections in autoimmune disease. Clin Exp Immunol 2009;155:1-15.

46. Samson M, Audia S, Martin L, Janikashvili N, Bonnotte B. Pathogenesis of giant cell arteritis: new insight into the implication of CD161+ T cells. Clin Exp Rheumatol 2013;31:S65-73.

47. Weyand CM, Schonberger J, Oppitz U, Hunder NN, Hicok KC, Goronzy JJ. Distinct vascular lesions in giant cell arteritis share identical T cell clonotypes. J Exp Med 1994;179:951-60.

48. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol 2013;9:731-40.

49. Mitchell BM, Font RL. Detection of varicella zoster virus DNA in some patients with giant cell arteritis. Invest Ophthalmol Vis Sci 2001;42:2572-7.

50. Nagel MA, Khmeleva N, Boyer PJ, Choe A, Bert R, Gilden D. Varicella zoster virus in the temporal artery of a patient with giant cell arteritis. J Neurol Sci 2013;335:228-30.

51. Nagel MA, White T, Khmeleva N, Rempel A, Boyer PJ, Bennett JL, et al. Analysis of Varicella-Zoster Virus in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis. JAMA Neurol 2015;72:1281-7.

52. Kennedy PG, Grinfeld E, Esiri MM. Absence of detection of varicella-zoster virus DNA in temporal artery biopsies obtained from patients with giant cell arteritis. J Neurol Sci 2003;215:27-9.

53. Bhatt AS, Manzo VE, Pedamallu CS, Duke F, Cai D, Bienfang DC, et al. In search of a candidate pathogen for giant cell arteritis: sequencing-based characterization of the giant cell arteritis microbiome. Arthritis Rheumatol 2014;66:1939-44.

54. Alvarez-Lafuente R, Fernandez-Gutierrez B, Jover JA, Judez E, Loza E, Clemente D, et al. Human parvovirus B19, varicella zoster virus, and human herpes virus 6 in temporal artery biopsy specimens of patients with giant cell arteritis: analysis with quantitative real time polymerase chain reaction. Ann Rheum Dis 2005;64:780-2.

55. Procop GW, Eng C, Clifford A, Villa-Forte A, Calabrese LH, Roselli E, et al. Varicella Zoster Virus and Large Vessel Vasculitis, the Absence of an Association. Pathog Immun 2017;2:228-38.

56. Pisapia DJ, Lavi E. VZV, temporal arteritis, and clinical practice: False positive immunohistochemical detection due to antibody cross-reactivity. Exp Mol Pathol 2016;100:114-5.

57. Rhee RL, Grayson PC, Merkel PA, Tomasson G. Infections and the risk of incident giant cell arteritis: a population-based, case-control study. Ann Rheum Dis 2016.

58. Cradock-Watson JE, Ridehalgh MK, Bourne MS. Specific immunoglobulin responses after varicella and herpes zoster. J Hyg (Lond) 1979;82:319-36.

59. Schub D, Janssen E, Leyking S, Sester U, Assmann G, Hennes P, et al. Altered phenotype and functionality of varicella zoster virus-specific cellular immunity in individuals with active infection. J Infect Dis 2015;211:600-12.

60. Draborg AH, Jacobsen S, Westergaard M, Mortensen S, Larsen JL, Houen G, et al. Reduced response to Epstein-Barr virus antigens by T-cells in systemic lupus erythematosus patients. Lupus Sci Med 2014;1:e000015,2014-000015. eCollection 2014.

61. Hanlon P, Avenell A, Aucott L, Vickers MA. Systematic review and meta-analysis of the sero-epidemiological association between Epstein-Barr virus and systemic lupus erythematosus. Arthritis Res Ther 2014;16:R3.

62. Draborg A, Izarzugaza JM, Houen G. How compelling are the data for Epstein-Barr virus being a trigger for systemic lupus and other autoimmune diseases? Curr Opin Rheumatol 2016;28:398-404.

63. Larsen M, Sauce D, Deback C, Arnaud L, Mathian A, Miyara M, et al. Exhausted cytotoxic control of Epstein-Barr virus in human lupus. PLoS Pathog 2011;7:e1002328.

64. Wutzler P, Bonanni P, Burgess M, Gershon A, Safadi MA, Casabona G. Varicella vaccination - the global experience. Expert Rev Vaccines 2017;16:833-43.

65. Ogunjimi B, Van Damme P, Beutels P. Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review. PLoS One 2013;8:e66485.

66. Weinmann S, Chun C, Schmid DS, Roberts M, Vandermeer M, Riedlinger K, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. J Infect Dis 2013;208:1859-68.

67. Hayashida K, Ozaki T, Nishimura N, Gotoh K, Funahashi K, Nakane K, et al. Evaluation of varicella zoster virus-specific cell-mediated immunity by using an interferon-gamma enzyme-linked immunosorbent assay. J Immunol Methods 2015;426:50-5.